

Biological implications of possible unattainability of comprehensive, molecular-resolution, real-time, volume imaging of the living cell

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Abstract

Despite the impressive advances in biological imaging, no imaging modality today generates, in a comprehensive manner, high-resolution images of crowded molecules working deep inside the living cell in real time. In this paper, instead of tackling this engineering problem in the hope of solving it, we ask a converse question: What if such imaging is *fundamentally* impossible? We argue that certain decoherence processes could be suppressed because the internal workings of the cell are not being closely “observed” in the quantum mechanical sense, as implied by the assumed impossibility of imaging. It is certainly true that the “wet and warm” living cell should not exhibit quantum behavior merely because of the lack of observation. Despite this, we plow ahead to see what *might* result from such absence of the outward flow of information. We suggest that chaotic dynamics in the cell could be quantum mechanically suppressed — a known phenomenon in quantum chaos, which is potentially resistant to various mechanisms for the emergence of classicality. We also consider places where experimental evidence for/against such a possibility may be sought.

1 Introduction

The central premise, or at least the central working hypothesis, of modern biology states that all forms of life, including us, are molecular machines. One might actually go further to assert that every form of life is essentially a *classical* molecular machine. A few qualifications are

needed for this latter version. First, without quantum physics we do not even have the stability of atoms and molecules, or their chemical reactions, not to mention the non-infinite specific heat of the vacuum. However, we may still be able to construct a classical model that describes interactions of molecules so that it successfully captures essential dynamics of the biological machine; much like the way workings of a transistor can reasonably be modeled with a few characteristic curves and/or equivalent circuits, hiding the “quantum-mechanical layer” — an abstraction layer in the computer engineering sense — of silicon atoms and electron waves underneath. Second, several emerging aspects of life being investigated under the heading of “quantum biology” challenge the view that life is basically classical.¹ These aspects include photosynthesis [1, 2] and magnetic sensing by European robins [3]. Although these phenomena are intriguing, it is fair to say that these are either a relatively short-time phenomenon where the associated energy quanta $\hbar\omega$ far exceed the thermal energy $k_B T$ as in the former, or a small-scale phenomenon occurring in — presumably, because the detail is not yet known — space spanning at most a few molecules, as in the latter. In other words, *in retrospect*, these quantum phenomena are found where they are expected, i.e. when the length or time scale is small, or only modestly larger than the scale where everyone would expect quantumness.

In this paper, we propose a new perspective to study the relevance of quantum mechanics in biology, possibly extending the arena where quantum physics plays a role. The main idea is the following. It is extremely difficult to invent an experimental method that enables comprehensive, molecular-resolution, real-time, volume-imaging (CMRV) of the living cell. By “comprehensive”, we mean that most molecules, as opposed to e.g. fluorescently labeled molecules that are a small fraction of the whole, can be observed simultaneously. By “volume imaging”, we mean true three dimensional (3D) imaging with the ability to see *internal* structures, which therefore goes beyond quasi-3D methods such as 3D topography enabled by the atomic force microscope (AFM). The stated extreme difficulty to invent a CMRV method is justified because otherwise somebody capable would have invented it, considering the utility such a CMRV method would offer to biology research. Turning this circumstance on its head, if the difficulty is not of practical but of *fundamental* character, then little information about the internal states of the cell is leaking to the outside environment because otherwise we would be able to measure it in principle. If this reasoning is correct, then the system is somewhat *isolated*, that in turn means quantum mechanically more coherent evolution is expected to a certain degree, which we later attempt to estimate.

The idea, that there is some connection between a biological object and quantum measurement on it, is actually nothing new: Already in 1932 Bohr discussed the connection noting that,

¹This may not be *the* consensus view. There is at least one biology textbook filled with quantum physics: W. Bealek, *Biophysics: Searching for Principles* (Princeton University Press, 2012).

in effect, a biological object might “hide its ultimate secrets” because a high-resolution measurement would destroy the object [4]. Fast-forwarding to modern times, Henderson noted that all high-resolution imaging methods in biology, be it X-ray diffraction or electron microscopy, are limited by radiation damage to the biological specimen [5]. Of course, a variety of methods — X-ray crystallography, cryoelectron microscopy, nuclear magnetic resonance (NMR) spectroscopy, scanning probe microscopy and “super-resolution” optical microscopy to name a few — have had remarkable successes in supporting biology research. However, these are complementary and each of these has a limited domain of applicability, for otherwise we would have a different or shorter list of methods in the above. Furthermore, as we will elaborate on later, each method has its own *fundamental* limits and whether or not CMRV will ever be possible is totally an open question. In the present work, we will eventually *assume* that CMRV is impossible for fundamental reasons, because we cannot prove it, in order to see if something interesting follows from the assumption, even though the present author has no idea one way or the other. Besides, if we were to assume the opposite case, actually developing a CMRV method would be more productive than indulging in speculations.

The idea, that quantum mechanics plays a significant role in biology at a larger scale than what are already mentioned, has also long history. Several authors that include prominent figures proposed since no later than 1967 that the human brain might be quantum mechanically coherent [6, 7, 8]. While the brain is outside the scope of the present work, a work that critically investigates the connection between the brain and quantum physics is relevant [9]. Briefly, the work concludes that the brain is such a dissipative system that dissipation-induced decoherence takes place far too quickly for any quantum coherence to survive. The question of whether or not the whole biological *cell*, as opposed to the whole brain, is quantum mechanically coherent has also been asked [10]. Their work contains a reasonable point that the internal workings of the cell are “observed” by the environment with possibly unconventional pointer states [11], to which the wavefunction “collapses”. Much as these studies are inspiring, it is perhaps fair to say that these are controversial at best, mainly because it is so unlikely to have quantum coherence in such “wet and warm” physical systems. To see this, consider the amount of effort it takes to build any quantum-enhanced instrument: That involves e.g. cooling, calibrating, vibration-damping, removing external noise, characterising intrinsic noise, and so on so forth. Nonetheless, we do not have a proof that quantum effects — of the sort we are discussing — do not appear in the wet-and-warm systems, because we do not fully understand the nature of the quantum-classical boundary.

The emergence of classicality is explained in several ways. First, classical mechanics is in a sense the short-wavelength limit of quantum mechanics and as such it emerges in exactly the same way as the way ray optics emerges from wave optics. In this view, classicality emerges

whenever the potential is smooth in the scale of the de Broglie wavelength.² Second, things become classical when the action S involved is much larger than $2\pi\hbar$. Loosely speaking, when a characteristic time scale of the system is τ , with the associated characteristic frequency scale $\omega \sim 2\pi/\tau$, then classicality requires $E \gg \hbar\omega$, where $E \sim S/\tau$ is a characteristic energy. Quantization manifests itself when the particle energy such as $\hbar\omega$, which tends to be larger for lighter particles, is larger than a characteristic energy scale of the system. Such characteristic energy scale may be the thermal energy $k_B T$ in a system embedded in an environment. This explains why most quantum experiments demand cryogenic temperatures, besides ones involving optical photons for example³. However, these conditions are still not complete: Microscopic quantum uncertainty could always be amplified to a macroscopic quantum uncertainty since quantum mechanics is linear, as exemplified by Schrodinger’s cat. The third way, in which classicality emerges, is decoherence due to interaction with the environment [12]. In this view, *we* as part of the environment get totally entangled with Schrodinger’s cat so that we do not notice the superposition.⁴ The importance of *isolation* of the system from the environment is emphasized here. For example, setting aside the subtlety due to the highly mixed nature of the states, NMR quantum computing works because of isolation, in spite of the condition $k_B T \gg \hbar\omega$. One way the amplification of minute quantum uncertainty happens drastically is when the system’s classical dynamics is chaotic; because the trajectory depends on the initial condition in an exponentially sensitive way. For example, amplification of quantum uncertainty to the macroscopic level in a surprisingly short time has been discussed with respect to very macroscopic objects including the Saturn’s satellite Hyperion [13]. It is only the interaction with the environment, partly in the form of impinging photons in this case, that keeps Hyperion classical. In the present work, we look into the possibility that the biological cell is classically chaotic and is not that well-observed by the environment as Hyperion is. Specifically, we consider possible delocalization of biological molecules in the cell, however provocative this possibility may seem.

This paper is organized as follows. A variety of biological imaging methods, established ones and also proposed ones, are discussed in Sec. 2 to show that the unattainability of CMRV

²Needless to say, quantum mechanics is not about classical waves. Hence this point alone cannot capture the entirety of the quantum-classical transition.

³This is only a rule of thumb. See e.g. F. Galve, L. A. Pachon, and D. Zueco, Bringing entanglement to the high temperature limit, *Phys. Rev. Lett.* **105**, 180501 (2010).

⁴If the reader is unsatisfied with this sentence, he/she may put themselves in the place of an external observer, so that “we” in the sentence become just a bunch of atoms. In this sense, the present work needs only the usual “shut-up-and-calculate interpretation”. A good explanation of quantum measurement that includes the observer as a part of the system is found in a lecture note by Preskill. See: J. Preskill, What is measurement?, Lecture Note, Ph 12b Quantum Physics, California Institute of Technology, 28 Jan. (2010). Web address: <http://www.theory.caltech.edu/~preskill/ph12b/Ph12b-measurement-28jan2010.pdf>

is a serious possibility. In Sec. 3 we first estimate how much “information” leaks out to the environment from the living cell. We then consider how these findings fit with what we know in quantum chaology including, in particular, quantum suppression of classical chaos. We consider potential observational or experimental consequences in case such quantum suppression of chaos is indeed at work. Section 4 concludes the paper. Throughout the paper we will use the SI system of units. Symbols c , ε_0 , \hbar and k_B respectively represent the speed of light, the vacuum permittivity, the reduced Planck’s constant and the Boltzmann constant, of which some have appeared already. Some symbols such as λ stand for multiple things (e.g. wavelength and Lyapunov exponent) in this paper to avoid cluttered presentation. The meanings of such symbols should be clear from the context. The technical presentation of this paper is kept at the elementary level because that is sufficient for our purpose. In particular, density operators are not used even in places where it may be natural to use them.

2 Biological imaging methods and their limits

In this section, we intend to show that *unattainability* of CMRV of the cell is a serious possibility. Beautiful results from biology research can be at the same time misleading because they give an impression that any biological measurement is possible.⁵ However, on a closer look one finds that each reported measurement was preceded by setting up particularly favorable conditions; each measurement method is associated with various fundamental limits; and more broadly, the progress in biological measurement has generally required new ideas besides persistent effort. At the risk of stating the obvious, if there is a fundamental obstacle towards CMRV, then CMRV is impossible.⁶

⁵At the optimistic end of the spectrum, it has been mentioned, for example, that an army of “nanobots” could go into someone’s brain to obtain data. It should also be noted that such a possibility has not been ruled out.

⁶It is unlikely that we actually can give a proof that CMRV is impossible even if it is. Indeed, not all impossibility should necessarily have a short and clever proof, like the one showing the impossibility to solve the halting problem in computability theory. However, a lengthy proof of the impossibility of CMRV could actually *exist*, which, however, may be beyond our reach in any practical sense. For example, given a reasonable laboratory size, say a cube with 10km edge length, there are only *finite* ways to place atoms in the laboratory if we regard two very similar atomic configurations, e.g. ones that differ only by a small amount of shifts in atomic positions (say, 0.1 Angstrom), to be the same. Almost all atomic configurations are hopelessly messy and unstable, but some configurations contain scientific equipment. However, if *all* configurations do not offer CMRV, then CMRV is impossible at least in a laboratory with a reasonable size. (For the sake of completeness, we note that even if such a CMRV configuration exists, it may not be *constructible* from a realistic initial state of the laboratory. Another minor point is that the size of the cube is set to be so large because we have the X-ray free electron laser in our mind.) Of course, if there is a *principled reason* why CMRV is impossible, which

We examine several biological measurement methods in the following. Obviously no single person is able to properly evaluate all these diverse methods, but it is hoped that the following assessment is a fair approximation to the fully competent ideal. A particular emphasis is on methods under development. While we also try to present a broad perspective, we do not intend to give a full review of established methods that are already widely used.

2.1 X-ray

X-ray methodologies used in biology are diverse. Some use soft X-rays, especially in the so-called “water window” at the wavelength of $2.34\text{nm} \sim 4.4\text{nm}$, and others use hard X-rays. Some use optical elements such as lens and mirror, while others including crystal diffraction are lensless. While there have been much progress in all of these [14], it remains true that the X-ray damages biological specimen generally more than electrons do for a given amount of structural information retrieved [5]. Simply put, X-ray photons are so energetic that they damage the biological specimen (mainly by photo-ionization). Hence the specimen is destroyed before a sufficient number of X-ray photons are collected to form an image. Whereas atomic-resolution structures of biological molecules are routinely obtained in X-ray crystallography because a large number of copies of the same molecules are involved, when it comes to single, unique objects such as a structure in a cell, X-ray methods are generally no better than the electron-based counterpart in terms of radiation damage [5].

The advent of the method called *flash X-ray imaging* [15, 16] makes an interesting twist to the above picture. The X-ray free electron laser (XFEL) invented long ago [17] has finally come to fruition after many years of effort and is capable of producing intense and short ($\sim \text{fs}$) X-ray pulses. The idea is that the inertia of atomic mass is no longer negligible at the femto-second time scale and hence the atomic nuclei stay where they are during the X-ray irradiation; despite the ionization of atoms due to the intense X-ray. Thus, a diffraction image can be recorded “before” the specimen is destroyed. Perhaps surprisingly to the uninitiated, phase information is generally in the diffraction pattern to allow for reconstruction [18, 19]. Nevertheless, $10^5 \sim 10^6$ identical copies of the molecule (or molecular complex) are still needed to get a 3D “near-atomic resolution” structure with currently foreseeable technology because each image is essentially 2D [20]. However, 3D imaging using a single copy of the specimen must be possible to begin to realize CMRV. (Those who think that CMRV is obviously impossible because the X-ray destroys the specimen, will find an argument based on *reconstruction* of the specimen below.) One way

certainly is a possibility, then the proof should be shorter than the brute-force kind mentioned above. For this viewpoint, see: D. Deutsch, *The Beginning of Infinity: Explanations That Transform the World* (Goodreads, 2011).

might be the use of tomography with multiple and almost simultaneous X-ray pulses from different angles, which seems to be a distant possibility. Another possible way is the use of “ankylography”, whose feasibility is under active research [21].

What are fundamental limitations of X-ray flash imaging, assuming that 3D image acquisition is possible? First, the larger the number of voxels is, the more intense the needed X-ray pulse is, in order to have enough number of photons to acquire enough information. However, the oscillating electric field of the X-ray field cannot be arbitrarily large for the following reasons. To observe atomic details with diffraction, we need X-ray with the wavelength of about the Bohr radius $a_0 = 4\pi\epsilon_0\hbar^2/m_e e^2$, where m_e is the electron mass. The standard approximation states that an electron bound to an atomic nucleus can be regarded free because the X-ray frequency is much larger than the “orbital frequency” of the bound electron. Hence classically we have

$$m_e \ddot{x} = eE \cos(\omega t), \quad (1)$$

where $\omega = 2\pi c/\lambda = 2\pi c/a_0 = cm_e e^2/2\epsilon_0\hbar^2$ is the angular frequency of the X-ray and E is the associated electric field amplitude. Plugging $x = -x_0 \cos(\omega t)$ in Eq.(1), we obtain $x_0 = eE/m_e \omega^2$, which is the motional amplitude of the electron being “shaken” by the X-ray field. Obviously, we start to have a problem when the X-ray field is so strong that x_0 approaches the Bohr radius a_0 , because then the electron approaches the neighboring atoms. Up to a numerical constant of the order of 1, the electric field at which $x_0 \sim a_0$ is $E_{\text{shake}} = m_e^2 c^2 e / 4\pi\epsilon_0 \hbar^2 \cong 10^{16} \text{V/m}$. The flow of energy J due to such an X-ray pulse is

$$J = \epsilon_0 E_{\text{shake}}^2 c \sim 10^{29} \text{W/m}^2. \quad (2)$$

On the other hand, Fig. 2 of Ref.[20] shows that the Linac Coherent Light Source (LCLS) has the X-ray brilliance of $\sim 10^{24} (\text{photon/s}/0.1\% \text{bw}/\text{mm}^2/\text{mrad}^2)$. A decent diffraction experiment should require 0.01% bandwidth monochromaticity and 0.1mrad beam divergence because both the monochromaticity and the beam divergence need to be roughly the wavelength divided by the specimen size, where the specimen size is $\sim 1\mu\text{m}$ here. (We do not consider methods based on high-bandwidth, ultrashort pulses.) Note that this assumption becomes increasingly shaky for larger specimens. Hence we have $J \sim 10^{18} \text{W/m}^2$ since each X-ray photon has energy of $\sim 12\text{keV} \sim 10^{-15} \text{J}$. On the other hand, Ref.[20] states towards the end that one needs $10^5 \sim 10^6$ specimens and 100-fold increase of the X-ray peak power to enable atomic resolution 3D imaging. Taking this at the face value, this would mean up to 8 orders of magnitude increase of the X-ray power might be needed if we want to do one-shot diffraction with a single specimen, resulting in a figure $J \sim 10^{26} \text{W/m}^2$. Comparing with Eq.(2), we have leeway of only a few orders of magnitude. This crude calculation suggests that at least more careful evaluation is desired for the flash X-ray method if it aspires to enable CMRV. Even assuming this is not a

problem, the electron-positron pair production begins at the Schwinger limit $E_S = E_{\text{shake}}/\alpha$, where $\alpha \cong (137)^{-1}$ is the fine structure constant [22]. This suggests a possibly general trend that higher power brings in new physics that has to be dealt with.

Second and more obviously, X-ray flash imaging is fundamentally destructive. This makes real-time imaging impossible, barring a rather strange possibility: We could, in principle, *reconstruct* the specimen each time, based on the recorded full structural information, possibly using a molecular-precision synthetic biology method. Such a method to reconstruct a biological specimen has been proposed [23], but as of now none has been demonstrated. Assuming that *this* is possible, one could in principle produce a movie of a biological process with a time step Δt if each reconstruction is followed by a waiting period Δt at room temperature before starting the next session of X-ray flash imaging, presumably by rapidly cooling the specimen to a cryogenic temperature (see discussions on cryoelectron microscopy below). Evidently, this is speculative at best and the minimum possible interval Δt may not be short enough, depending on scientific questions being asked. Since this notion will appear repeatedly in this paper, we call this method reconstruction-based cryogenic stop-motion photography (RCSP).

2.2 Electron microscopy

Despite the impressive progress in biological electron microscopy (EM), the resolution-limiting factor of biological EM remains to be *radiation damage* to the specimen by the probe electrons themselves.⁷ Hence the situation is qualitatively similar to the case of X-ray. However, flash imaging with electrons seems somewhat contrived at least at the fundamental level since the electrons are fermions and moreover they electrostatically repel each other. In this subsection, in spite of the growing relevance of e.g. serial block-face scanning EM (SEM) in the brain “connectmics” research [24], we focus on transmission EM (TEM) that is relevant in molecular and/or atomic scale imaging.

The art of biological TEM is multifaceted. The traditional methods use protocols such as plastic embedding and heavy metal staining. The reason for the latter is that the Coulomb force from the atomic nuclei is the main scattering mechanism in TEM. These protocols work

⁷A historical note: Whereas R. P. Feynman expected electron microscopy to be an important tool in biology, saying “It is very easy to answer many of these fundamental biological questions; you just look at the thing!”; D. Gabor responded to L. Szilard’s suggestion of biological electron microscopy with dismissive “What is the use of it? Everything under the electron beam would burn to a cinder!” As noted in the main text, the tension between these two views persists today. These quotes are taken respectively from: R. P. Feynman, There’s plenty of room at the bottom, presented at Annual Meeting of APS, Pasadena (1959). Transcript: J. Microelectromech. Syst. **1**, 60 (1992); R. M. Glaeser, Cryo-electron microscopy of biological nanostructures, Phys. Today **61**, 48 (2008).

excellently and led to many important discoveries at the scale of organelles, but they introduce artefacts at the molecular scale. Thus, cryoelectron microscopy (cryoEM) [25, 26] was introduced in order to enable molecular or atomic scale resolution in biological TEM. First, cryoEM uses vitrified specimens at cryogenic temperatures (typically the liquid nitrogen temperature) and hence the specimen can be placed in a vacuum. Second, in order to prevent the growing ice crystals from destroying fine biological structures, the method uses liquid ethane, to which the thin specimen is rapidly dropped. Liquid ethane tends to have less bubbles than liquid nitrogen does and hence allows for a better thermal contact. Hence the specimen is rapidly vitrified and the water remains in the glassy state. It is widely believed that the specimen prepared as mentioned represents a biologically relevant, natural structure. However, the contrast is very weak in cryoEM because typical biological specimens contain mostly light elements. Moreover, one can use only a limited dose of electrons of at most $\sim 10^3 e/\text{nm}^2$ because of *radiation damage* to the specimen caused by the very electrons used for imaging. Hence, the resolution is limited by shot noise, which is a fundamental consequence of the electron being a particle.

Before proceeding, we comment on TEM in the broader context. TEM has been used also in materials science since the beginning, where the resolution had long been limited by lens aberration. The aberration has finally been corrected in the 90's [27, 28], fifty years after Scherzer showed possible solutions [29]. Atomic resolution images are now routinely obtained for beam-*insensitive* inorganic specimens. Furthermore, a study using aberration-corrected TEM presents beautiful pictures of organic molecules in the carbon nanotube [30]. Low-voltage, aberration-corrected electron microscopes have been developed around the globe, enabling imaging of beam-sensitive specimens [31, 32, 33]. However, few things should be kept in mind. First, aromatic molecules or ones with a similar structure, such as the nanotube, are very stable and highly resistant against radiation damage; while most biological molecules are not. Second, the specimen used in Ref.[30] is very thin, whereas molecules of biological interest can be as large as 30nm and the vitrified specimen must be thick accordingly. However, a thicker specimen requires higher beam energy to have electron transmission at all. Moreover, the higher energy electron beam is associated with more inelastic scattering events and resultant secondary electrons, which in turn cause radiation damage. In short, much as the pictures of organic molecules in nanotubes are beautiful, that does not mean that the same quality of images can be obtained in other situations such as cryoEM of biologically interesting molecules.

At least two ways to bypass the radiation damage problem have been successfully developed and these are established methodologies in structural biology today [34]. Both of these are based on averaging to improve the signal-to-noise (S/N) ratio using multiple copies of the same molecule. The first method is electron crystallography that often use 2D crystals, which are not easy to come by. The second method is called "single-particle analysis", where many identical

molecules are prepared in vitreous ice *without* crystallizing them. Although each molecule has a random orientation, approximate orientations of the molecules may be determined from the noisy raw data, thus allowing us to average images of similarly-oriented molecules, resulting in a better S/N of the estimated structure. This in turn allows us to obtain a better estimation of molecular orientations by fitting the estimated structure to the raw data. Iterating this, one can increasingly refine the computed structure; although obviously there are pitfalls associated with this clever method that almost magically pulls out useful data from very noisy raw data. The uninitiated reader should note that intricate structures obtained with cryoEM found in the scientific literature are likely to be the result of such averaging and data processing. In such cases, these structures do *not* represent the raw resolving power of cryoEM. The resolution of raw data remained to be $5 \sim 10\text{nm}$ because of radiation damage at least until recently, when improved electron detectors began to be widely used [35].

Ideas for potential future improvements to cryoEM are in the pipeline. The so-called “interaction-free measurement”, which is capable of detecting an photon-absorbing object without actually getting photons absorbed, was first proposed long ago [36]. Subsequently, it was *significantly* refined so that the failure probability can be brought down arbitrarily close to zero [37], and finally its use in biological EM was proposed [38]. While interaction-free measurement is inspiring, its use is limited when it comes to distinguishing two semi-transparent objects, as opposed to distinguishing the vacuum and a semi-transparent object [39]. However, this aspect is important because one would like to distinguish, e.g. protein and water in cryoEM. Another proposed way to improve cryoEM is the use of superconducting qubits to achieve measurement at the Heisenberg limit, rather than at the the shot-noise limit [40, 41]. This latter scheme may improve the resolution of cryoEM but it will likely fall short of achieving the atomic resolution.⁸ The simple reason, after all, is that imaging methods using electrons are fundamentally destructive. A possible way to get around this difficulty would be the use of RCSP. Again, this possibility is speculative at best.

2.3 NMR

NMR occupies a unique position in biological imaging because it does not belong to the usual category where the incident wave scattered by a specimen is measured. The frequency ν of the electromagnetic wave is at most on the order of 1GHz and hence the photon energy $h\nu$ is at

⁸A somewhat outdated “review” of this particular proposal is presented in Sec. I of: H. Okamoto, Measurement errors in entanglement-assisted electron microscopy, Phys. Rev. A **89**, 063828 (2014). On a slightly personal note, this author began suspecting the impossibility of CMRV after spending a decade to learn that improving cryoEM at all, even *in theory*, is rather hard; although an appreciable improvement turned out to be possible at least in theory.

most $\sim 10\mu\text{eV}$, which is far smaller than energy scales associated with an X-ray or an electron beam, or even $k_B T$ at room temperature. Consequently, specimen damage is minimal, if not zero, in NMR and this represents perhaps the most attractive aspect of NMR. The downside of this is the weak signal to be detected, which typically translates to a slow data acquisition rate.

We first broadly review relevant aspects of NMR. As is well known, volume imaging with NMR is routinely done today by magnetic resonance imaging (MRI), where the spatial resolution is typically $\sim 1\text{mm}$. Using dedicated instruments, the MRI resolution has been pushed down to $\sim 1\mu\text{m}$ for small specimens [42]. In structural biology outside the standard domain of imaging, NMR has widely been used to determine protein structures, using a solution containing a massive number of the same molecule of interest. However, NMR is generally not suitable for large proteins basically because the recorded spectrum becomes too complex to interpret. NMR is associated with a large “bag of tricks” and reviewing NMR spectroscopy in a decent way is firmly beyond the scope of this paper. Hence, in what follows, we focus on methods that seem relevant to CMRV.

One method that aspires to enable CMRV is magnetic resonance force microscopy (MRFM) [43, 44]. The method has been improving ever since its introduction, resulting in a relatively recent demonstration of biological imaging with resolution $< 10\text{nm}$ [45]. A conceptually similar yet distinct method utilizing the nitrogen-vacancy (NV) center in diamond has also been introduced recently [46]. This latter technology, NV magnetometry (NVM), has several distinct usages but here we focus on the one relevant to CMRV, which is nano-scale MRI. Does MRFM/NVM represent a possible path to achieve CMRV? Since future prospects of the methods are nicely summarized in Ref.[47] at least in the case of MRFM, here we point out only few potential obstacles. First, MRFM/NVM is a *scanning* NMR method and hence, combined with the fact that the weak signal requires integration for a long time, it is slow. This makes real-time imaging difficult, unless RCSP is employed. High-resolution MRFM/NVM measurements are likely to eventually require cryogenic temperatures to reduce thermal noise and to prevent diffusion of biological molecules, making the method non-real-time in the ordinary sense anyway. Second, MRFM/NVM employs a magnetic field gradient $\partial B/\partial z$ as in the conventional MRI. The magnitude of the gradient $\partial B/\partial z$ determines the spatial resolution Δz , in such a way that the field difference

$$\Delta B = \frac{\partial B}{\partial z} \Delta z \quad (3)$$

corresponds to the attainable frequency resolution Δf through the gyromagnetic ratio. What are fundamental frequency resolution limits Δf ? First, there is the frequency broadening due to dissipation, that lowers the Q value of the oscillator in MRFM, or in the case of NVM that

determines the phase coherence time of the NV center. It is hard to know if such dissipation is intrinsic or extrinsic. Second, there is no motional narrowing in solid state NMR, unlike in bulk liquid NMR. Consequently, almost inevitably we have inhomogeneous broadening Δf (besides intrinsic broadening due to dissipation) of the resonance peak [48]. This broadening translates to a largely uncontrollable/unknowable frequency shift of individual nuclear spin (typically that of hydrogen) placed in the inhomogeneous environment, in localized measurements such as ones performed in MRFM/NVM. The spatial resolution limit is reached when such a shift Δf matches ΔB in Eq.(3). On the other hand, the magnetic field gradient is typically produced by a tiny, but strong, magnet placed nearby the biological specimen. Naturally, the field gradient $\partial B/\partial z$ decays quickly as the distance from the magnet increases. This in turn means that we lose resolution fairly quickly as the depth from the specimen surface increases. Hence volume imaging is hard with MRFM/NVM. Consequently, even if MRFM/NVM will eventually be capable of atomic resolution imaging, that will likely be confined at near the surface of the specimen. While there are theoretical proposals [49] to address this problem, at present no proposal claims to achieve atomic resolution imaging for the specimen of the size of the whole cell, i.e. $> 1\mu\text{m}$.

2.4 Scanning probe microscopy

Among many variants in the category of scanning probe microscopy (SPM), we focus on AFM here, because of its obvious relevance. In AFM, the size of the force can be in the pN range and the oscillation amplitude of the cantilever can be $\sim 0.1\text{nm}$. Hence, the energy scale is $\sim 10^{-22}\text{J}$, which is less than $k_B T$ at room temperature. This makes AFM nondestructive. A remarkable image of an organic molecule was obtained in 2009 [50], despite under a condition that does not seem to be extendable to general biological imaging. In the following year, another remarkable result visualizing a walking molecule in real time with a high-speed AFM was reported [51]. This has *almost* realized CMRV, except the “volume imaging” part. Is there a way to do volume imaging with AFM? *In theory*, one might remove a thin layer after another as in serial block-face SEM, perhaps with an ion beam of helium or argon, to study the 3D structure at a cryogenic temperature. However, this will come at the price of losing true real-time imaging at room temperature, even if comprehensive molecular resolution imaging on etched surfaces is possible. This latter imaging incorporating RCSP appears possible *in principle*. However, effects such as charging of the surface may well make it impossible, as perhaps most people experienced with imaging a thick piece of insulator with AFM could attest.⁹ Another

⁹What initially appears to be a mundane, practical kind of difficulty may well be fundamental impossibility if it persists despite our best effort. See also the argument in Footnote 6. This may cast a shadow of doubt on

limiting factor in AFM is dissipation, which appears to be a ubiquitous obstacle in advanced measurement in general, that broadens the resonance peak of the cantilever. In summary, while AFM is likely to be nondestructive, it is fundamentally surface specific. While more research is definitely desirable, at present no reliable path along the use of AFM can be identified towards realizing CMRV.

2.5 Optical microscopy

Optical microscopy is unsurprisingly a vast subject and we discuss only a few topics here. Our discussion begins with far-field methods, followed by near-field methods. Finally, we comment on the recently-introduced expansion microscopy.

Super-resolution microscopy methods are among those that are designed to break Abbe’s diffraction barrier $d = \lambda/2n \sin \alpha$ [52]. Essentially all super-resolution methods rely on the use of fluorophores. One group of super-resolution methods exploits certain nonlinearities of the fluorophore: In laymen’s terms, if a fluorophore is excited suddenly above certain threshold intensity of the excitation light, one may adjust the excitation light beam intensity so that the fluorophores are excited only at the very center of the beam.¹⁰ The second group of method is based on the observation that one can determine the *center* of a point-like optical image from a fluorophore to a precision much better than Abbe’s limit by fitting e.g. a gaussian intensity profile. This, by itself, does not allow for identifying multiple optical sources within the diffraction limit, but if there is a way to identify each optical source — for example by color, but the “signature” can be more subtle — then one can determine the position of each source to a precision that far exceeds Abbe’s limit. These are fabulous and practical ideas. That said, there are some obstacles towards CMRV. First and most obviously, only fluorophore-tagged molecules can be observed and hence the “comprehensive” part of CMRV is not satisfied. Even if all different kind of molecules were tagged with different fluorophores, aside from the slowing down of the data acquisition rate, questions remain as to whether such a system would behave as the natural ones do. Second, at present the cell to be imaged are typically fixed chemically, and fluorophores are overexpressed [53]. This again raises a question as to whether the system is natural enough. Third, optical bleaching of fluorophores defines the allowable photon dose. This is a resolution limiting mechanism similar to the limiting factor in X-ray diffraction and biological TEM. Moreover, the typical optical intensity used in super-resolution imaging can be quite high for the biological specimen itself. Despite all these, improvements exploiting

the notion that what is possible in principle can be impossible in practice.

¹⁰This is an oversimplification to the extent that it is quite wrong, but this author believes that this picture captures the essential idea.

quantum optical effects have been demonstrated in optical microscopy in general [54, 55].

Next, we discuss near-field methods. These methods include the scanning near-field optical microscope (SNOM), which is a variant of scanning tunneling microscope (STM) [56]. First, this is a scanning method and intrinsically slow. Second, SNOM captures evanescent field for high resolution information and hence it is surface specific. These two points, especially the latter, render SNOM hopeless as a candidate for CMRV. However, the advent of the “perfect lens” [57] presents an interesting opportunity where *all* evanescent field, including ones deep inside the specimen, could be collected to form an image. Nevertheless, the evanescent field does decay exponentially. For ensuing discussions, the reader is referred to Ref.[58].

Finally, we take a look into expansion microscopy introduced recently [59]. This is an innovative method that, instead of making the specimen *look* bigger, makes the specimen *actually* bigger. However, this method is fundamentally destructive, which is analogous to cryoEM. Hence, even if it proves to be a comprehensive molecular-resolution volume-imaging method in the future, it must incorporate RCSP to enable CMRV. To reiterate, RCSP is at best a speculative possibility.

Two final remarks are in order. First, Henderson notes [5] that neutrons damage the specimen little for a given elastic scattering signal compared to the X-ray photons and electrons. He further notes that the problem is of a practical character, which is that the brightness of available neutron sources are many orders of magnitude smaller than what would be needed and hence atomic resolution neutron microscopy is “impossibly far off”. It remains to be seen if this difficulty is indeed of a practical character, or this is a fundamental problem masquerading to be a practical one (see Footnote 9). Additionally, deuterization needed for this imaging modality may significantly affect the functioning of the cell [60]. Second, discussions regarding acoustic microscopy are presented in the next section.

To summarize, X-ray and electron-beam methods are fundamentally destructive and they would require RCSP, a highly speculative possibility at present, to enable CMRV. On the other hand, NMR-based methods, while non-destructive, appears too slow to enable real-time imaging unless RCSP is employed. Moreover, these methods appear to be fairly surface specific for reasons discussed above. In scanning probe microscopy such as AFM, true-3D imaging appears out of reach although interesting real-time results have been obtained for molecules on the surface. Finally, in optical microscopy, fluorophores are required in a condition that may be far from the physiological condition, casting doubt as to whether optical microscopy will ever enable CMRV. Thus, we conclude that the present state of the art of microscopy does *not* reject the hypothesis that CMRV is fundamentally impossible.

3 Quantum physical implications of the unobservability

In this section, we investigate the impossible-CMRV hypothesis and its consequences from a more theoretical standpoint. Before delving into details, we sketch the main ideas, which come from quantum physics as mentioned in the Introduction: If CMRV is impossible, comprehensive information about the internal working of the cell is not leaking to the outside environment — and this seems reasonable also from the contraposition of the statement. This consequence implies that some degrees of freedom corresponding to the internal workings of the cell are not being observed in the quantum mechanical sense. This leads to spreading of the quantum wave packet associated with these degrees of freedom, provided that these are subject to chaotic time evolution.

To be specific, consider a possibility that the position of a whole molecule, for example a protein molecule in the cell, is quantum mechanically smeared to an extent to be discussed. The protein molecule under the present discussion should not be labeled with a fluorophore because that would localize the molecule under conditions that enables observations. Note that we are not talking about the position of an electron or a proton, which *are* expected to behave quantum mechanically from the common sense perspective. Of course, the protein molecule is constantly hit by the surrounding molecules — and hence being “observed”, meaning that its quantum state should “collapse” to a quasi-position-eigenstate almost continuously [9]. However, *those* surrounding molecules are also quantum objects whose wavefunctions tend to spread,¹¹ which are in turn “observed” by yet other molecules and so on. Naively, such a chain of observations could lead to accumulation of positional errors (Fig. 1(a)). In the end, however, no comprehensive information about the positions of these highly entangled molecules goes outside the cell under the assumption that CMRV is impossible.

Furthermore, the number of molecules in the cell is basically proportional to its volume. The amount of information to specify the positions of all the molecules could be roughly proportional to the volume if many of those molecules move chaotically and their positions cannot be deduced. On the other hand, we expect the information leakage rate, which allows an outside observer to determine the positions of the molecules, to be basically proportional to the surface area of the cell. (Throughout this paper, we use the term “information leakage rate” in a loose sense, since giving a precise definition will not be useful at the present stage.) Hence, in this sense, molecules in a larger cell are more isolated because of the small surface to volume ratio of the cell. This argument, by itself, leads to an apparently unacceptable suggestion that larger objects are more quantum, but the strangeness of the argument does call for a close

¹¹In this introductory paragraph, we loosely talk about the “wavefunction” of each molecule. Needless to say, to be correct we should be talking about multi-particle states.

examination.

One might ask: “Okay, let us assume, for the sake of argument, that the positions of some molecules are somehow delocalized in the cell. However, what would be the *consequence* of it? The thermal de Broglie wavelengths of the molecules are so short that even supposing that quantum interference was at work, the “fringe spacing” would be extremely small — not to mention that we do not have enough statistics to form a “fringe pattern” in the first place. Doesn’t this mean that the squared wavefunction is indistinguishable from an incoherent classical probability distribution?” To address this question, we will point out later that quantum mechanical suppression of otherwise chaotic classical motion of molecules might manifest itself, despite the short wavelength involved.

In the end, unsurprisingly, these seemingly “crackpottery” ideas of delocalized molecules cannot be convincingly supported in the present work. However, we will find that these ideas cannot be easily dismissed either. That we cannot conclude one way or another is actually astounding, because *all* molecules’ positions in the cell are well-localized in space according to the conventional wisdom. In what follows, we will attempt to make the foregoing argument more precise and, where possible, semi-quantitative.

3.1 Preliminary considerations

To fix thinking, we first consider *Deinococcus radiodurans*, a single-celled life form that is so-named because it has a high radiation tolerance [61]. For our purpose, however, its tolerance to the vacuum is more important. Suppose that one *Deinococcus radiodurans* cell floats in a vacuum chamber in a zero-gravity lab on the orbit. We may furthermore suppose that the vacuum chamber is at the near-zero temperature and the cell is in the process of being cooled down via radiative cooling, although it is still at room temperature. This “setup”, while expensive practically, simplifies conceptual considerations. Setting aside exotic possibilities, essentially all information that the cell “communicates” to the outside world is sent as infrared (IR) thermal radiation. For a large enough vacuum chamber we can forget about the evanescent IR field because it is exponentially suppressed (See Sec. 2.5) and hence we may consider only traveling IR waves. Abbe’s limit then tells us that a very small amount of information about the workings in the cell is communicated to us.

One question regarding the above setup is whether or not the positions of some molecules in the cell is quantum mechanically well-defined or not. It is actually rather likely that the position of the whole cell is smeared. After all, Young’s interference pattern has been experimentally observed for the C_{60} molecule [62]. In the experiment, the position of the C_{60} molecule is highly delocalized, whereas the relative positions of the constituent C atoms are certainly well defined.

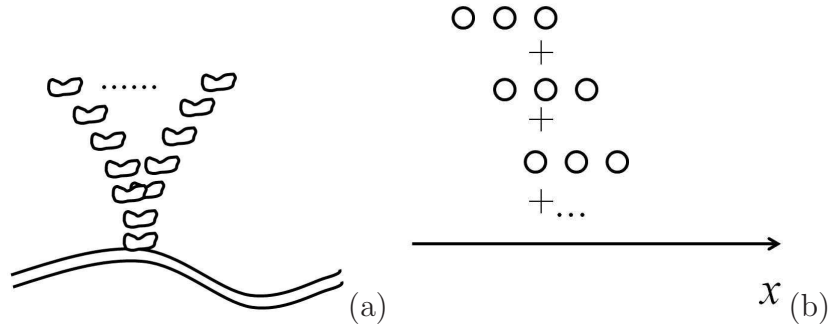


Figure 1: Two *conceptual* drawings are shown here. (a) A chain of molecules in the cell interacting via a position-dependent potential. The bottom lines represent a lipid bilayer. While the molecule at the surface is well-localized, molecules in the deeper positions may not be. Note that this is a very naive picture and should be taken with a grain of salt. (b) A 1D crystal comprising 3 atoms. The center-of-mass position of the crystal is quantum mechanically smeared, whereas the relative positions of constituent atoms are well-defined. Each row represents a localized (with respect to the position of the *entire* crystal) quantum state to be superposed. The horizontal axis represents a spatial coordinate, the x -axis.

(The experiment in Ref.[62] is well-controlled because a number of C_{60} molecules are needed to generate statistics to see the fringe pattern. In the present situation, we are not talking about a repeatable experiment to *prove* quantumness of the system. Rather, we are talking about whether the cell's *actual* position is quantum mechanically smeared or not.¹²) Hence, a better question would be whether or not *relative* positions of the molecules in the cell are quantum mechanically smeared. In the case of C_{60} molecule or a piece of metal, it is safe to say that the relative positions of atoms are not smeared beyond the conventionally acceptable values (Fig. 1 (b)).

Before proceeding, we note that IR radiation from the cell does give away some information about the state of the cell *thermodynamically*. This point is easier to see for a piece of cooling metal, rather than the biological cell, floating in the cryogenic, zero-gravity vacuum chamber. Measurement of IR radiation allows us to calculate the amount of reduction of energy ΔE of the piece of metal due to radiating. The entropy $S(E)$ decreases with the decreasing energy E , meaning that the number of available states decreases, thus increasing our certainty

¹²According to one view, a quantum state describes the state of our knowledge (epistemological state) rather than the state associated with an object (ontological state). See e.g. C. A. Fuchs and A. Peres, Quantum theory needs no ‘interpretation’, Physics Today, pp.70, March (2000). Here we are minimally interested in these interesting discussions; and the *essence* of our argument is intended to be independent of interpretational issues, or lack thereof.

about the state of the system, assuming the principle of equal *a priori* probabilities of statistical mechanics. Hence, provided that we know the system’s hamiltonian eigenstates already, measurement of ΔE gives us information; although the IR radiation contains basically zero structural information because of the long wavelength and Abbe’s limit. Obviously, this sort of “general information” is not of much interest for us. To see this point better, next consider a microprocessor chip computing some mathematical function with power supplied by a small battery, again floating in a vacuum, enclosed in a tiny metallic case. Measurement of IR radiation emanating from the metallic box would tell us mostly about the amount of energy that the battery has lost, *not* the mathematical function that the processor is computing.

3.2 Chaotic dynamics as a defining property

If we assume that relative positions of some molecules in the cell is quantum mechanically smeared, then there should be some property that distinguishes the cell from the C_{60} molecule or a piece of metal. This is because relative positions of atoms are well-defined in the latter systems.¹³ For the sake of argument, we put forward the notion that the defining property of systems like the biological cell is that the system dynamics is classically chaotic. (We do not have to be fussy about the precise definition of “classically chaotic”. It may be considered to mean that the classical *simulation* of the cell using the molecular dynamics (MD), whatever variant that may be, is chaotic.)

The intuitive picture behind this proposal comes from Hamiltonian classical mechanics, where a volume in the phase space is preserved; but the volume is exponentially stretched and folded in a complex way in chaotic systems. This means that, in a quasi-classical picture, the initial wave packet (or more relevantly, the Wigner distribution), even if it is associated with minimal quantum uncertainty at the beginning, will be stretched and folded as well, unless an external observation collapses the wavefunction. Dynamical variables, e.g. the relative positions of molecules in our case, get quantum mechanically smeared in the absence of such external observations. The well-known phenomenon of quantum suppression of chaos would set in, when the spread of the wave function reaches the maximum possible range and start interfering itself. Everything in this paragraph has already been discussed in the literature [13].

An immediate counterargument to the above proposition, that the cell is classically chaotic, may be that the Reynolds’ number relevant to the cell is so small that things do not seem chaotic at all. Although nothing substantial can be said at present, we point out that the

¹³Roughly speaking, a drop of superfluid helium is similar to a piece of metal because its state *is* ordered, albeit in the reciprocal space. However, a drop of water could present an interesting case. See the following discussion.

biological cell is far more complex than a uniform fluid. There are several biological aspects known to have a very sensitive character. First, the retina is known to respond to only a few photons [63]. Second, some molecular signaling pathways involve only a few molecules in the entire cell [64]. Third, a chaotic model of a nerve cell, which is biologically motivated, has been proposed [65]. These aspects may differentiate biological systems from a drop of water, although properties of water is not fully understood. Evidently, however, more needs to be studied about whether biological systems are classically chaotic or not. In the followings, we will *assume* such chaotic behavior in order to see where this assumption leads us to.¹⁴

We consider the possibility that the cell has chaotic dynamics that leads to quantum suppression of chaos, which is a quantum phenomenon. To sharpen our thinking, consider a toy chaotic pendulum with a magnet, which obviously is totally classical [66]. What distinguishes the cell and the toy pendulum? The latter behaves classically because the pendulum is “observed by the environment” (air molecules, ambient photons etc.) before its wavefunction spreads. What if we enclose the pendulum in a solid metallic box, or a cryogenic vacuum chamber if needed, so that an external observer is not able to extract any information about the pendulum position, as in the impossible CMRV situation? Will the pendulum position quantum mechanically spread? It has been argued that even the orientation of Hyperion the satellite will be quantum mechanically smeared if unobserved [13]. In practice, of course, minute mechanical friction, or an eddy current generated by the magnet, *inside the box* will cause energy dissipation that depends on the position of the pendulum, which effectively constitute an observation in the quantum mechanical sense, thus localizing the pendulum position.¹⁵ Note that the dissipated energy is stored in degrees of freedom of e.g. the lattice vibration of the material of the system, which are not chaotic. Here we consider a possibility, without much support at present, that there are *not* so many non-chaotic degrees of freedom in the cell to dissipate the energy of the chaotic motion. Put another way, possibly a large portion of degrees of freedom of molecules in the cell are themselves chaotic and interacting with each other, constituting one big and complex chaotic system without many non-chaotic degrees of freedom left to dissipate energy. Hence, if quantum suppression of chaos, of the sort that is discussed in this paper, is to take place, the system under question is *necessarily microscopic*; as possibly in the case of a molecular machine of life. This is reminiscent of the contrast between macroscopic rubber balls in a box (which quickly fall down to the bottom) and air molecules in a box (which bounce around

¹⁴Such an assumption has been used in a speculative yet interesting argument on the free will. See: S. Aaronson, The Ghost in the quantum Turing machine, in *The once and future Turing: Computing the world*, Ed. by S. B. Cooper and A. Hodges (Cambridge University Press, 2016). Further study is desirable, especially in connection with the simulation hypothesis possibly supplemented with the 5-minute hypothesis.

¹⁵While this assertion sounds reasonable, it is difficult to justify the claim unless we delve into specific details of the setup.

forever). In this view, the distinction between the two concepts *macroscopic* and *microscopic* is not vague and is indeed qualitative — it amounts to whether or not degrees of freedom at smaller scales, to which energy is dissipated, exist.¹⁶ Simply put, it amounts to whether friction exists or not. Note that modern microelectronic gadgets do not fall into the category of “microscopic machines” in the sense just mentioned, even though some of these are chaotic [67].

One might question the above possibility that there are not many non-chaotic degrees of freedoms in the cell to dissipate energy into. About 40-60% of cell content is water [68] and it *seems* to provide many degrees of non-chaotic freedom. While not much can be said about this at present, we make a few remarks for future considerations. First, the entropy S of water at 25°C is 70J/mol · K [69] and

$$\frac{S}{N_A k_B} = \ln W = 8.4, \quad (4)$$

where N_A is Avogadro’s number. The number of states W for a single water molecule is therefore $W = e^{8.4} \cong 5 \times 10^3$. This is a large number, but it should also be kept in mind that a wavefunction spreads exponentially in chaotic systems, although *only* in chaotic systems. Second, water exhibits quantum behavior in confined space [70], which appears not dissimilar to the space between crowded molecules in the cell. Third, several interesting coincidences about the water properties have been pointed out [71]. Namely, the “energy broadening” $\delta E \cong h/\delta t$ due to the hydronium ion lifetime $\delta t \cong 0.2\text{pS}$ in water is comparable to $k_B T = k_B \cdot 298\text{K}$, suggesting the quantumness of proton motion. Additionally, the speed of sound is comparable to the thermal velocity of protons $\sqrt{k_B T/m}$ at room temperature, where m is the proton mass. This suggests that thermal proton motions easily become collective. While these three points do not constitute anything solid, they do suggest that our understanding of water, especially under biological conditions, is still developing and water cannot easily be regarded as providing only external, non-chaotic degrees of freedom to make things classical. In this view, water is *unlike* the solid material of the toy chaotic pendulum.

Another perspective to see chaotic dynamics in relation to quantum mechanics is the following. The state of a quantum system collapses to an eigenstate of an observable after a measurement according to the textbook quantum mechanics. However, if one sees the system comprising the quantum system and the measurement apparatus *from the outside*, the whole system, if isolated, generally remains in a superposed state even after the measurement. Do the constituent states interfere? The standard answer is no, because the measurement record prevents these from interfering. However, there is nothing that prevents interference from

¹⁶The degrees of freedom at smaller scales considered here should be *soft*. For example, deformation of nuclei can safely be ignored because nuclei are hard, or in other words, has a large characteristic energy scale.

happening if the measurement record is erased by unitary time evolution. Such quantum interference does not usually happen in the macroscopic realm because the “measurement record” may be imprinted, for example, on a human brain or on the photons flying away from the Earth. In other words, in the standard macroscopic case, the distinct branches of quantum evolution do not interfere because the measurement record is somewhere in the universe.¹⁷ However, things could be subtle if the whole system is in a small, closed box. What if the universe (or the box) is so small that it does not have a sufficient number of bits to record the variety of things that have happened? In this “saturated” situation, distinct events that result in an identical measurement record would interfere. Of course, the state of the system does collapse if someone makes a measurement from the outside. However, suppose that a complex chaotic system inside a box has classically distinguishable states A_1, A_2, \dots, A_n , that differ only in the part that is deep inside the box. Let the states B_1, B_2, \dots, B_m be another set of classically distinguishable states on the surface of the box, that have natural measurement values (e.g. values of pressure at each position on the surface of the box). Each state A_i evolves into a complex superposition of many states, which include most of B_1, B_2, \dots, B_m as the “surface component” in the tensor product, due to chaotic dynamics. Hence, a measurement at the surface of the box does not reveal which of the states A_1, A_2, \dots, A_n the system started with. This means that the “measurement records” going outside are themselves completely jumbled up because of the chaotic dynamics.¹⁸

Thus far we have been thinking mostly about the quantum nature of molecular motions. What about electronic degrees of freedom? The electronic part only determines the potential energy functions for the positions of nuclei as far as conditions for the Born-Oppenheimer approximation are met. Needless to say, this approximation breaks down when, e.g. plasmon-phonon coupling is significant. Although such circumstances may well play a role in biological systems, considerations of these are beyond the scope of this paper.

3.3 The amount of information leakage

In the above-mentioned case involving *Deinococcus radiodurans*, essentially the only channel through which information about the internal workings of the cell leaks is thermal radiation. We

¹⁷In a sense, the *purification* procedure on a mixed quantum state may not be a purely mathematical procedure — it amounts to physically go look for the measurement record in the world. However, that would be much more difficult than e.g. gathering spilled liquid.

¹⁸This is reminiscent of the quantum error correction codes, where the logical qubit is encoded in physical qubits in a jumbled way so that measurements on a *part* of physical qubits do not reveal the content of the logical qubit. Note that this analogy goes only so far because the feedback part is missing in merely-chaotic quantum systems.

estimate the information content of it to gain further theoretical insights about the impossible-CMRV hypothesis. First, we regard thermal photons as independent. The question is whether internal motion of the cell can be seen via the thermal radiation through an optical microscope. The answer is obvious but we do quick calculation anyway. We are interested in molecular details and we take 10nm as the representative size of a large biological molecule. (For comparison, the prokaryotic ribosome has the size of about 20nm.) We want to see things at least with this resolution $\lambda_0 = 10\text{nm}$. We consider the best case, where the emissivity is 1 at all wavelength. Since we have $h\nu_0 \gg k_B T$ at this wavelength $\lambda_0 = c/\nu_0$ and at $T = 300\text{K}$, Planck's law for the spectral radiance $B_\nu(\nu, T)$ is approximated as

$$B_\nu(\nu, T) \cong \frac{2h\nu^3}{c^2} e^{-h\nu/k_B T}, \quad (5)$$

where $\nu > \nu_0$. Multiplying this with the solid angle $\cong 4\pi$ into which radiation is emitted, and the specimen surface area $l^2 \cong 10(\mu\text{m})^2$; and divide with the photon energy $h\nu$ (note that we do not intend to do precise calculation and hence largely skip calculation of the numerical factor), we get something that represents spectral density of photon number flux from the cell

$$S(\nu, T) \cong \frac{8\pi\nu^2 l^2}{c^2} e^{-h\nu/k_B T}. \quad (6)$$

We integrate this with respect to ν from $\nu_0 = c/\lambda_0 = c/10\text{nm}$ to infinity to obtain the number of “high-resolution” thermal photons per unit time

$$\dot{N} \cong 8\pi \left(\frac{l}{\lambda_0}\right)^2 \nu_0 \frac{\alpha(\alpha+2)+2}{\alpha^3} e^{-\alpha} \cong 8\pi \left(\frac{l}{\lambda_0}\right)^2 \frac{\nu_0}{\alpha} e^{-\alpha}, \quad (7)$$

where $\alpha = h\nu_0/k_B T = 5 \times 10^3 \gg 1$ for $T = 300\text{K}$ and $\nu_0/\alpha = k_B T/h = 6\text{THz}$ is a characteristic frequency of the thermal photons. While the pre-exponential factor is $\cong 10^{18}\text{Hz}$, the exponential factor makes \dot{N} completely “zero”, so that we would not get any high-resolution photons even if the photons were collected for the age of the universe $\sim 10^{17}\text{s}$.

Next, we consider another scenario, in which photons are correlated. This could be the case because the *Deinococcus radiodurans* cell is isolated in a vacuum and its thermal radiation is not “random” but faithfully represents the internal dynamics of the cell that could involve something similar to “down conversion”, in which short wavelength excitations (presumably something akin to phonons) is converted to IR photons emitted. The resolution beyond Abbe's limit by the factor n , i.e. $\cong \lambda/n$, is conceivable if n entangled photons are involved and a photon detector that detect n -photons together, whose existence is possible in principle, is available [72]. Now, suppose most optimistically that our thermal photons are entangled in any way we wish. Since the thermal photon wavelength at $T = 300\text{K}$ is $\lambda_{th} = c/\nu_{th} = 5 \times 10\mu\text{m}$, we suppose

the existence of $n \cong 5 \times 10^3 (= \alpha)$ photons in the GHZ-like state to obtain the resolution of $\sim 10\text{nm}$. We call the group of n photons a “photon bunch”. For the sake of simplicity, we suppose all thermal radiation is at the wavelength λ_{th} . Stefan-Boltzmann’s law suggests that the total power P from the *Deinococcus radiodurans* cell is

$$P \cong \sigma l^2 T^4 = 5 \times 10^{-8} \text{W}, \quad (8)$$

where σ is the Stefan-Boltzmann constant. Dividing this with the thermal photon energy $h\nu_{th} = 4 \times 10^{-21} \text{J}$, where $\nu_{th} = k_B T/h$, we obtain the IR photon current $\dot{N} \cong 1 \times 10^{13} \text{Hz}$. The current is $\dot{N}' \cong 2 \times 10^9 \text{Hz}$ in terms of the photon bunch. Hence, $\sim 10^7$ photon bunches make each image if we assume a video rate image acquisition of $\sim 10^2 \text{Hz}$. This number of photon bunches results in a 100×100 pixel image with $\sqrt{10^3} \sim 30$ dynamic range. This probably is *just* acceptable. However, recall that we made an *exceedingly* optimistic assumption that the thermal photons are entangled in a way we want. It appears quite certain that photons are much less correlated.

Overall, in this rather special case of the *Deinococcus radiodurans* cell floating in a cryogenic vacuum chamber on a spacecraft, it is quite certain that information leakage is minimal. If it turns out that the internal dynamics of the *Deinococcus radiodurans* cell is not so chaotic, one could replace the cell with a more usual, possibly more chaotic, cell that is protected from the vacuum with the recently introduced nano-suit [73]. Hence, in view of supporting the impossible-CMRV hypothesis, the present argument based solely on the IR-radiation is more tenable, though less realistic, than the rest of the argument in this Sec. 3.3.

We move on to a more realistic scenario, leaving the scenario of the *Deinococcus radiodurans* cell floating in a cryogenic vacuum chamber on a spacecraft. The cell is in a standard laboratory in this realistic case, interacting with the surrounding medium or other cells. The “communication channel” is no longer restricted to IR radiation and it involves direct “mechanical” contacts between the cell under investigation and the surrounding environment. Considerations on *phonons* seem more appropriate in this situation. Since the typical sound velocity is 5 orders of magnitude smaller than the velocity of light, the parameter α in Eq.(7) is much smaller than 1 here. Moreover, we expect no significant acoustic impedance mismatch since everything is rather soft and has similar density. Hence there could be substantial high-resolution information going out through the phonon channel.

Shouldn’t the reader stop reading this and start developing a high-resolution biological *phonon* microscope [74]? In fact, acoustic microscopes using superfluid helium have achieved resolutions at around 10nm [75]. Hence the usefulness of the phonon channel in biological imaging under cryogenic conditions remains to be seen, especially in combination with RCSP. However, when liquid water is involved as in a living specimen, the frequency of sound waves with

the wavelength 10nm is about 100GHz assuming the sound velocity of 10^3m/s . A resolution-limiting factor, among others, in this more typical ultrasonic imaging is attenuation of the sound at high frequencies, or nonlinearity at high power used in an attempt to increase the signal to noise ratio [76]. The standard imaging theory is useless in such a region of large attenuation and nonlinearity, where e.g. kinematic approximation is invalid. Hence, we cannot use arguments or gedankenexperiments that employ the concept of a microscope to estimate the information leakage.

We need to take a different approach to estimate information leakage through the supposedly nonlinear and dissipative phonon channel. Since phonons are about mechanical degrees of freedom, consider the following gedankenexperiment: To every tiny patch of the surface of the cell in question, we attach a nano-needle that is a sensitive force sensor (or a displacement sensor), as shown in Fig. 2 (a). Hence we get *all* mechanical information emanating from the cell, although whether or not this gedankenexperiment can actually be done is a separate question (see Footnote 9). The question is whether or not we can infer the positions of *all* the molecules in the cell from this measurement. Intuitively, this strikes us as impossible, especially when the size of the cell is large, because more “information “ is generated in the cell than information that can be extracted through the surface because surface-to-volume ratio tends to be small in a large system. Does this intuition stand up to simple scrutiny?

Of course, the above argument does not apply to a piece of metal for example, because of the known atomic structure. However, in a chaotic system knowledge of the initial condition, even supposing we knew that, would not allow for knowledge at later times. In other words, the number of chaotic “branching” per unit time in the cell is relevant here because we are interested in whether or not it is greater than the “measurement bandwidth” of the setup in Fig. 2 (a).

Our situation corresponds to a quantum circuit shown in Fig. 2 (b) in “quantum information science” terms. The quantum circuit represents a program for a large scale quantum computer that simulates the dynamics of the cell. The upper portion of qubits, which will be referred to as *internal qubits*, represent the degrees of freedom corresponding to the molecules inside the cell, so that the qubits cannot be measured directly. On the other hand, the lower portion of qubits, to be referred to as *surface qubits*, collectively represent molecules on the surface of the cell and these are constantly measured. (After a measurement, the qubits should be set to the measured values, but we surmise that the values after the measurement are not important and the qubits could as well be reset. The molecules on the outer surface are constantly pushed and pulled by the external environment anyway. This point will not affect the rest of the discussions.) The big boxes containing many quantum logic gates in the circuit represent the chaotic dynamics under which the cell evolves.

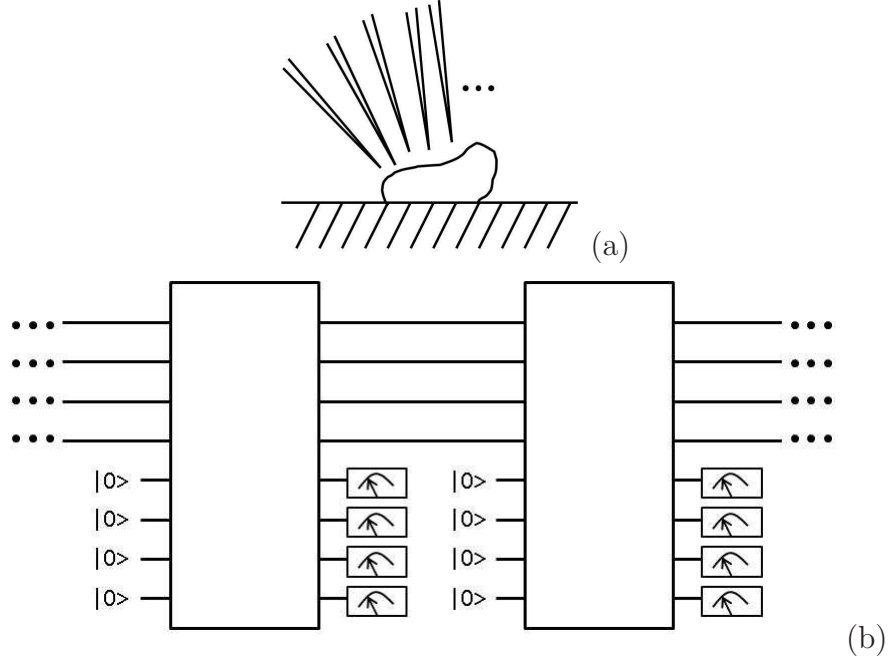


Figure 2: (a) Comprehensive mechanical measurement on a biological cell. The cell (the blobby object) is on the substrate, to which a number of force/displacement sensors (the needle-like objects) are placed. The substrate may have to incorporate many sensors as well. (b) A quantum circuit model of the cell. The lower portion of the qubits, corresponding to the degrees of freedom on the cell surface, are constantly measured (measurements are represented by the meter objects) and reset to the state $|0\rangle$. The upper portion, corresponding to the internal degrees of freedom of the cell, is only indirectly accessible from the measurement apparatus, i.e. from the surrounding environment. The boxes contains quantum circuit describing the chaotic time evolution. The number of qubits is arbitrary, but here we show 8 qubits for clarity.

General arguments only take us so far. The internal dynamics of the cell — or in terms of the quantum circuit shown in Fig. 2 (b), the circuit structure inside the large box — has to be considered to estimate the amount of information leakage. The reason is simple: For an extreme example, the state of the internal qubits is certainly unobservable if no quantum logic gate connects the internal qubits and the surface qubits. On the other hand, consider an internal qubit A corresponding to a degree of freedom pertaining to a molecule deep inside the cell, which interacts indirectly with a surface qubit Z through a chain of qubits, which roughly represents a chain of molecules that has something akin to nearest-neighbor interactions. Suppose that in this chain of qubits $\{A, B, C, \dots Z\}$, the interaction is such that qubit A controls qubit B with the controlled-NOT (CNOT) gate, and then qubit B controls qubit C, and so on, eventually reaching the surface qubit Z. Further suppose that initially the qubit A is in the symmetrically superposed state

$$|\psi_A\rangle = \frac{|0\rangle + |1\rangle}{\sqrt{2}}, \quad (9)$$

where $|0\rangle$ and $|1\rangle$ correspond to two localized states of the internal molecule, and the rest of the qubits are in the state $|0\rangle$. Then we end up with a GHZ state, on which if a measurement on the surface qubit Z is made with respect to the basis $\{|0\rangle, |1\rangle\}$, then the entire wavefunction collapses. Hence this is the opposite extreme, in which the internal information of the cell is obtainable by measuring the surface molecules. Note that this second situation is at odds with the impossible-CMRV hypothesis, except that this particular quantum circuit may not allow for *comprehensive* internal information acquisition because of the existence of other qubits etc. There are of course cases in between. For example, if each of the above CNOT gate is replaced with a similar gate that rotates the controlled qubit only with a small angle ε as opposed to the angle π , the probability amplitude for the state in which the qubit Z is in $|1\rangle$ is roughly ε^{N-1} , where N is the number of qubit in the chain. One may regard this as exponential suppression of information leakage that would effectively imply the impossibility of CMRV.

Thus, these considerations suggest that detailed knowledge of the biological machinery in the cell is needed to estimate the information leakage rate. Can we go beyond this useless statement, at least to give a “ballpark guesstimation”? This question is hard to answer and we only make several crude attempts in the followings.

First, we show that the above-mentioned exponential suppression is quite unlikely to happen in the cell for the following reasons. Consider two molecules colliding each other in the cell. Assume for simplicity that these molecules are effectively rigid. If the collision is weak enough to enable the exponential suppression, it should leave the final quantum state of the two molecules largely overlapped with the initial state. This may be seen most clearly by the “caricatured” (in the sense of the word used by Zurek [13]) version appeared above, where the angle- ε CNOT

gate illustrates the weak molecular collision. On the other hand, an actual molecular collision should typically transfer energy of the order of $k_B T$ simply because the molecules have such a range of varying energy. However, there are many “energy levels” within the width $k_B T$, resulting in a nearly complete change of the quantum state upon collision. (Needless to say, the positional degrees of freedom of the molecule have continuous energy levels. However, they are *effectively* discretized to the “energy levels” with a spacing $\sim \Delta E$, where the value of ΔE corresponds to the positional localization of the molecule.) This is how a version of $\hbar\omega \ll k_B T$ comes up here, which is good because any discussion lacking emergence of this aspect would be missing something important. Nevertheless, this shows that the idea of exponential suppression occurring in the cell is incorrect.

Barring the possibility of weak collision between the molecules, what kind of “models” of the cell can we profitably consider? First, consider a model, in which neighboring molecules exchange their quantum states upon collision, much like the SWAP gate in a quantum circuit. Hence in this model, a piece of quantum information random walks and hence the information will have leaked when it hits the surface of the cell. When considering this, we imagine localized molecules colliding with each other exchanging their states, which is admittedly at odds with the hypothesis that the molecular positions are delocalized to cause quantum suppression of chaos. Let us ignore this point and plow ahead. Observe that this whole process is like a random walk, in which changes of the direction are caused by intermolecular collisions. Hence, the “diffusion constant” associated with the process is probably not too different from the actual diffusion constant of biological molecules in a cellular environment. Past measurements [77] have shown that such diffusion constants are roughly in the range of

$$D \cong 10^{-6} \text{cm}^2/\text{s} = (1\mu\text{m})^2 / (10\text{ms}). \quad (10)$$

Another model we consider employs a “random unitary operator” as a single-step discrete time evolution operator. In other words, each big white box in Fig. 2 (b) is such a random unitary operator. We mention a few caveats before we start. First, our definition of the “random unitary operator” R is that the absolute values of all the upper triangular matrix elements and the diagonal matrix elements are independent and identically distributed (i.i.d.) random numbers, while the phases of all upper triangular matrix elements are drawn from the uniform distribution in $[0, 2\pi)$. In addition, R of course obeys the unitarity relation $R = R^\dagger$. It must be noted that the usual definition of “random unitary operator” is much more sophisticated in order to make certain properties invariant under relevant transformations [78, 79]. However, our discussion is intended only to make a first dent into the problem and hence we do not use advanced concepts. See, e.g. Ref.[80] for an example of more advanced treatment. Second, there are “exponentially many” states in the Hilbert space (although technically the number is

uncountable infinity) and hence there are correspondingly many unitary operators that bring $|0\rangle$ to these states. Evidently, most of these unitary operators contain exponentially many quantum logic gates. Therefore, the actual unitary operator that govern cellular time evolution should not be randomly drawn from all the possible unitary operators, but from a “polynomially large” set.¹⁹ We will largely ignore this issue. Third, since the operator is random, our argument ignores geometric structures of the cell. It does not, for instance, take the 3-dimensional nature of the space. A randomly distributed nearest-neighbor CNOT gates in a 3-dimensional lattice, for example, would constitute a better model but that is beyond the scope of the present work.

Having mentioned these caveats, we proceed to use the quantum circuit model incorporating the random unitary operator. (Note that the general quantum circuit model can describe *any* quantum system, up to mathematical technicalities.) To be specific, let the number of all qubits and the internal qubits in Fig. 2 (b) be n and m , respectively. Hence the number of surface qubits is $n - m$. Let N be $N = 2^n$ and likewise $M = 2^m$. Basis states are written as $|b_1 b_2 \cdots b_n\rangle = \bigotimes_{i=1}^n |b_i\rangle_i$, where b_i , whose value is either 0 or 1, represents the value of i -th qubit, whose state space is spanned by $|0\rangle_i$ and $|1\rangle_i$. The label i starts from 1 to n and points to a surface qubit when $n - m < i$. An alternative way to represent a basis state is $|k\rangle$, where binary representation of the integer k is $b_1 b_2 \cdots b_n$, so that $0 \leq k \leq N - 1$. We normalize the state vectors so that $\langle k|l\rangle = \delta_{k,l}$. The complex coefficient of the basis state $|k\rangle$ is written as c_k . The random unitary operator R representing each big white box in Fig. 2 (b) has matrix elements $R_{k,l} = \langle k|R|l\rangle$. We formulate the problem as follows. Let the first qubit $|b_1\rangle_1$ represent the internal dynamics of interest, so that $|0\rangle_1$ and $|1\rangle_1$ represents the position of the molecule under consideration. Suppose that the position of the molecule is already spread due to the chaotic dynamics and hence the state is $(|0\rangle_1 + |1\rangle_1) / \sqrt{2}$. Assume that all qubits are disentangled at the beginning. Our “encoding” of the molecular quantum states into the qubit states is such that disentangled qubits translates to having a molecular quantum state that is in accordance with the conventional wisdom — that all molecules are localized classically (except the one described by qubits including the first one) and these are not quantum mechanically entangled. Then, without loss of generality, we set all other qubit in the state $|0\rangle_i$, where $i = 2, 3, \dots, n$. Hence, the quantum state we initially have is

$$|\Psi\rangle = c_0|00\cdots 0\rangle + c_1|10\cdots 0\rangle, \quad (11)$$

where $c_0 = c_1 = 1/\sqrt{2}$. This is a superposition of the positional states of the molecule being at two different places. The question is how well this superposition of equal amplitude is preserved after a single step of time evolution and a measurement on the surface qubits. We apply the

¹⁹Here we abuse the terminology from computational complexity theory in order to present a rough idea.

unit-time-step evolution operator R to Eq.(11) to obtain

$$\{R_{0,0}|0\rangle + R_{1,0}|1\rangle + R_{2,0}|2\rangle + \cdots\}/\sqrt{2} + \{R_{0,1}|0\rangle + R_{1,1}|1\rangle + R_{2,1}|2\rangle + \cdots\}/\sqrt{2}, \quad (12)$$

where N terms in the first set of braces represent the state evolved from the first term in Eq.(11) and likewise terms in the second set of braces arose from the second term in Eq.(11). A measurement on all $n - m$ surface qubits results in only M remaining terms in the each set of braces. Up to a normalization factor, we have

$$\begin{aligned} |A\rangle + |B\rangle = & \{R_{X,0}|X\rangle + R_{X+1,0}|X+1\rangle + R_{X+2,0}|X+2\rangle + \cdots\} \\ & + \{R_{X,1}|X\rangle + R_{X+1,1}|X+1\rangle + R_{X+2,1}|X+2\rangle + \cdots\}, \end{aligned} \quad (13)$$

where X depends on the measurement outcome and the states $|A\rangle, |B\rangle$ represent respectively the right-hand-side terms in the first and second set of braces. There are several questions to consider. First, how orthogonal are $|A\rangle$ and $|B\rangle$? Since the matrix $R_{k,l}$ is “random”, we first make an overall normalization to the matrix so that the average of the square of the absolute value is $\langle |R_{k,l}|^2 \rangle \approx 1/M$. Hence $|A\rangle$ and $|B\rangle$ have approximately the unit length. We obtain $|\langle A|B \rangle| \cong 1/\sqrt{M}$ unless $R_{k,l}$ obeys an unusual probability distribution, because the summation goes in the “random walk” fashion due to the random phase of $R_{k,l}$. Hence, $|A\rangle$ and $|B\rangle$ are approximately orthogonal. The second question is how well the equality of the probability amplitudes of $|A\rangle$ and $|B\rangle$ is preserved. This depends on the probability distribution, to which $R_{k,l}$ obeys. For example, if $|R_{k,l}| = 1/\sqrt{M}$ holds exactly and $R_{k,l}$ only have random phases, the equality of the amplitudes of $|A\rangle$ and $|B\rangle$ is preserved perfectly. In general, the equality of the probability amplitudes is preserved approximately, again unless $R_{k,l}$ obeys an unusual probability distribution. The third question is whether or not the relative phase between $|A\rangle$ and $|B\rangle$ is preserved. As can be verified easily, the relative phase is not preserved at all. It is unclear if such an introduction of random phase affects the quantum suppression of chaos. This circumstance resembles to, if we take an analogy from condensed matter physics, e.g. a coherent electron wave under a fluctuating external magnetic field, as opposed to a dissipative motion of the electron that gets entangled with the lattice degrees of freedom. The reason is that the states $|A\rangle$ and $|B\rangle$ remain largely coherent and do not evolve into a mixed state despite the phase noise.

Although the above analysis seems to support the notion that the information leakage is small, this result should be taken with a grain of salt. First, the random unitary operator which brings *all* states to *all* states in one time step is not at all realistic. The real-world time-evolution is likely to be sparse with respect to a suitable basis. Second, the above results, such as the difference in probability amplitudes between $|A\rangle$ and $|B\rangle$, depend only on M and

not on N . This unacceptable aspect comes probably from the fact that we used a rudimentary definition of “random unitary matrix” and hence further studies are needed.

3.4 Quantum suppression of chaos

In view of the above difficulty in estimating the information leakage rate, it is even more difficult to estimate how the suppression of chaos in the cell might play out. Hence we will be brief. We continue to assume that the dynamics of the cell is classically chaotic and that the information leakage rate determines how the quantum state of the cell collapses. The process is, in a sense, competition between the chaotic expansion of the quantum state in the positional space, which occurs with the rate proportional to characteristic Lyapunov exponents, and the collapse of the quantum state by external observations that occurs with the rate that is essentially proportional to the information leakage rate. We do not know how many unstable degrees of freedom exist in the classical model of a biological cell — even a “ballpark guesstimation” of which is beyond the scope of the present work — and also do not know the various positive Lyapunov exponents associated to these degrees of freedom. A preliminary study could start once these are more or less known. Then we might model the process of “external observation” by collapsing one randomly-selected degree of freedom, for example, setting the “spread of the wave function” (SWF) associated with the degree of freedom to the initial value. When the SWF reaches its maximum value, which will be referred to as the “range” below, in one of the degrees of freedom, we may regard that as beginning of quantum suppression of chaos [13].

To see the crudest physics, consider a simplified system, in which all the positive Lyapunov exponents λ_i and the range L_i of the associated dynamical variables x_i are the same for all N unstable degrees of freedom. Hence $\lambda_i = \lambda$ and $L_i = L$ for all $i = 1, 2, \dots, N$. Oversimplifying freely, the equations of motion that we consider is a set of independent differential equations

$$\dot{y}_i = \lambda y_i, \tag{14}$$

where y_i is roughly the SWF associated with the i -th degree of freedom. (For example, the x_i -dependence of the wavefunction at some given time may approximately be $\simeq e^{-x_i^2/2y_i^2}$.) Hence we have $y_i = y_0 e^{\lambda t}$, where t measures the elapsed time since the last wavefunction collapse and y_0 is the characteristic size of the wavefunction right after the collapse. Note that the wavefunction spreads fully in the allowed range L of the variable x_i at $t = t_L \cong (1/\lambda) \ln(L/y_0)$ and the suppression of chaos begins. Note the insensitivity of t_L on L and y_0 . Oversimplifying further, suppose that each degree of freedom is “measured” with a time interval $\Delta\tau$. Then we see that it is a sort of “speed competition” between the exponentially expanding SWF and its collapse caused by the external observations. We might conjecture that this speed

competition results in two phases *in general*, such that the chaotic expansion dominates in one phase ($t_L \ll \Delta\tau$) while measurement-induced collapses dominate in the other ($t_L \gg \Delta\tau$), depending on the rate of the external observation $\Delta\tau^{-1}$.

3.5 Possible places to find experimental evidence

It is rather easy to *imagine* a highly conclusive experimental proof for large-scale quantumness in a biological system.²⁰ However, at present we cannot propose an experimental scheme that would generate evidence for/against quantum suppression of chaos in a biological cell with a reasonable degree of certainty. Hence, we content ourselves with considering where we might find at least circumstantial evidence.

First, there may be thermodynamic evidence. Recall that von Neumann entropy does not increase in an isolated quantum system, even in a system apparently out of equilibrium [81]. This apparent paradox is resolved when interaction with the environment is taken into account. In a usual system, the positional degrees of freedom is subject to einselection, i.e, environment-induced superselection. Hence, the exponential spread of the state in a chaotic system is reflected as a linear increase of entropy as far as the system is observed frequently enough. This process is obviously affected if quantum suppression of chaos is at work in the cell. We check some numbers: Human body comprising $\sim 10^{13}$ cells [82] produces heat flux on the order of 100W, suggesting that each cell produces $\dot{Q} \cong 10\text{pW}$ of heat flux. From the relationship

$$\overline{d}Q = TdS = k_B T \cdot d(\ln W) = 0.69k_B T \cdot d(\log_2 W), \quad (15)$$

where S is entropy, we can compute how many bits of uncertainty are produced in a cell per unit time as

$$\frac{d(\log_2 W)}{dt} = \frac{\dot{Q}}{0.69k_B T} \cong 10^9 \text{bit/s}, \quad (16)$$

where $T = 300\text{K}$. If the size of a cell is roughly $(1\mu\text{m})^3$, then the above calculation suggests that 1 bit of uncertainty, or chaotic spread by a factor 2 in our picture, is generated in a volume $(1\text{nm})^3$ every second. For instance, if this rate turns out to be too small for the supposedly chaotic motion in the cell, this number would support the hypothesis that quantum suppression of chaos is going on in the cell. However, all this depends on how many chaotic

²⁰For example, it would be an almost conclusive proof if a man factors large integers super-fast. More seriously, a detection of a violation of any version of Bell's inequality by measuring quantities at two separate places on a biological system will also constitute a strong proof. It would indeed be conclusive if the separation of two measurement events is spacelike. However, even an impossibility of signaling by the speed of some biologically relevant phenomena (nerve signaling, speed of sound, "speed" of molecular diffusion etc.), as opposed to the speed of light, in an experiment would constitute a rather convincing demonstration.

degrees of freedom there are and what Lyapunov exponents are associated to these. Hence further investigations into the classical dynamics in the cell are desired.

Are we too eager to invoke quantum suppression of chaos in the above, when heat is simply generated from another form of energy? As a sanity check, we consider a light bulb. Suppose that the tungsten wire has a diameter $d = 50\mu\text{m}$, resistivity $\rho = 25\mu\Omega \cdot \text{cm}$ at temperature $T = 10^3\text{K}$, in which a current $I = 1\text{A}$ flows. One can compute how much heat flux \dot{Q} one tungsten atom contributes, taking into account the volume-per-atom $\Delta V = 1.6 \times 10^{-29}\text{m}^3$. Carrying out similar computation, we obtain at $T = 10^3\text{K}$

$$\frac{d(\log_2 W)}{dt} = \frac{\dot{Q}}{0.69k_B T} = \frac{\rho \Delta V}{0.69k_B T} \left(\frac{I}{\pi d^2/4} \right)^2 \cong 10^2 \text{bit/s}. \quad (17)$$

What does this number mean? This has nothing to do with the chaotic spread of a wavefunction. Instead, it reflects the following situation: The “motion” of a tungsten atom is excited by the electric current, thus having more quantum states available. Then the atom releases heat to the environment, with which “uncertainty” is thrown away because a smaller number of quantum states are available after releasing heat. In the case of chaotic systems, the entropy increase due to the spread of wavefunction is understood only in terms of interaction with the environment, that converts the initially pure (for the sake of argument) state to a mixed state. Hence it is natural to consider that the measurement process itself injects the necessary energy to the chaotic degree of freedom. In the biological cell under our hypothesis, this energy comes presumably from internal degrees of freedom that “monitors” the chaotic degree of freedom. Eventually, the heat must be released to the environment surrounding the cell. Also recall that, at the same time, we proposed the notion that there are not many degrees of freedom that monitor the putative chaotic degrees of freedom.

Second, isotope substitution may generate some hints, although this approach seems less promising. The idea is that quantum suppression of chaos may be itself suppressed if internal degrees of freedom that monitor the putative chaotic degrees of freedom (see Sec. 3.2) are made more effective. While water molecules are quantum mechanically identical particles (disregarding proton hopping etc.), partial deuterization of water makes the molecules less identical, which could change the ability to “observe” the dynamics inside the cell because of the increase in the available number of states, if only slightly. It is known that cells malfunction with heavy water [60] and mammals die when they are fed heavy water extensively [83]. Of course, these facts by themselves do not constitute fair evidence for our purpose.

Third and finally, if functioning of the cell, or functioning of life more broadly, critically depends on quantum suppression of chaos, then classical simulations, e.g. MD simulation, of biological cell should fail. A difficulty with this “approach” is that there should be myriad of other things that could make simulations fail. (Conceivably, we may be able to “steal” a method

from the “quantum supremacy” research to establish the quantumness [80].) Conversely, falsification of the existence of quantumness in the cell, providing that is the case, would be relatively straightforward by successful classical simulations. On a related note, RCSP described in Sec. 2.1 “classicalizes” the system at each time step separated by Δt and this is in a sense similar to classical simulation. Hence, RCSP should also fail under the hypothesis that quantum suppression of chaos is at work in the cell.

4 Conclusions and afterthoughts

Are some molecules in a biological cell quantum mechanically delocalized so much so that quantum suppression of chaos sets in? Surprisingly, our conclusion is that *we do not know*. This is surprising because the answer according to the conventional wisdom is resounding *no, all molecules are localized*. The present study is built on quantum chaology research, in which it is known that even huge objects can evolve into a quantum mechanically smeared state if the system is classically chaotic, and if the system is not observed (i.e. without decoherence). We argued that experience shows that it is difficult, or perhaps impossible, to measure the internal states of the cell comprehensively, real time, at molecular resolution and in true 3D. This suggests that external observers cannot observe some internal states of the cell. We argued that in the cell, unlike other chaotic systems that have been studied, it *could* be that there are *not* many non-chaotic degrees of freedom that acts effectively as an internal observer. The reason is that the cell could be a *microscopic* molecular machine without many extraneous degrees of freedom. We argued that, if that is the case, the chaotic, exponential spreading of wavefunction may outpace the rate at which decoherence effects “collapse” the wavefunction. We argued that, in spite of the short wavelength of the matter wave and the physiological temperature involved, quantum effects, if they exist, could manifest itself through the known phenomenon of quantum suppression of otherwise classically chaotic dynamics. We showed that, if the phenomenon is actually there, it might leave its fingerprints in some places although none of the suggested “fingerprints” will be conclusive.

We reiterate the above summary, this time from another viewpoint of how the biological cell, a warm-and-wet physical system, *could* evade various mechanisms of the emergence of classicality. The first mechanism of the emergence of classicality is similar to how ray optics emerges from wave optics, making the position of an object well-defined. In our case, however, a quantum wavepacket could spread fast enough because of the putative chaotic dynamics, which in turn causes interference eventually, although the de Broglie wavelengths of molecules are far shorter than the length scale associated with the potential. The second mechanism works when energy associated with the system, such as $k_B T$, is sufficiently large to obscure individual

energy quantum $\hbar\omega$. However, it is known in quantum chaology that quantum effects manifest itself even when the energy of an object is very large and the associated de Broglie wavelength is short, *if* the object is well-isolated. This brings us to the third mechanism of decoherence. We argued that if there are a sufficient number of chaotic degrees of freedom in the volume of the cell, information about the motion of these degrees of freedom may not leak out effectively because of the limited surface area of the cell. This could make the degrees of freedom somewhat isolated, which is a prerequisite for the suppression of decoherence.

Before moving on to considerations on possible consequences of the quantumness we have been discussing, we consider a couple of alternative scenarios. First, it should be pointed out that chaotic dynamics is not the only way to amplify quantum uncertainty, or to spread the wavepacket. As exemplified by the Schrodinger’s cat argument, sensitive measurement apparatus will also do the job. Dynamics of the cell could simulate chaotic dynamics if some molecular systems that effectively act as quantum measurement apparatus are in the cell. Note that, however, technically such a system would not necessarily be chaotic in the strict sense because chaoticity requires exponential divergence of trajectories at essentially everywhere. Nonetheless, such strict chaoticity is not required in the argument presented in this paper. Second, it could be that CMRV is impossible *not* because there is no information leaking out. Instead, it might be that the leaked information is hopelessly jumbled up at the cell surface and “reconstruction” of the desired information is next to impossible. If this is the case, quantum coherence needed for the quantum suppression of chaos does not exist. At the same time, this possibility would raise the hope that CMRV is possible after all. However, it should be mentioned that this scenario appears to be at odds with the “scaling” idea that the surface area may not be large enough to transmit information arising from the number of “chaotic information sources” that is presumably proportional to the volume, as the system size increases. Nonetheless, it may be that chaotic information sources are not independent but entangled to each other, which is similar to the case of the chain of CNOT gates discussed following Eq.(9).

We next consider possible consequences of the truth or falsehood of the hypothesis that molecules are delocalized in the cell. If it turns out that all molecules in the cell are well-localized as the conventional wisdom states, then there will be no change in our conception of biological systems. Things may have to be reconsidered, however, if it turns out that some molecules are delocalized and quantum suppression of chaos is at work. For example, future research programs of simulating the whole cell by MD simulation will have to take this effect into account, or at least keep the effect in mind. It is currently unknown whether or not the quantum-mechanically suppressed chaotic systems can be efficiently simulated with a classical computer. If it is impossible to classically simulate such systems efficiently, that might represent an obstacle

in the field of computational biomodeling.²¹ On the “brighter” side, such impossibility will make quantum computing research more relevant to life science than it already is. More speculatively, future artificial “synthetic biology” systems might perform otherwise intractable computations in this case.

Suppose that the hypothesis under our study — the classically chaotic dynamics of molecules in the cell is suppressed quantum mechanically — is actually true. Are there any further biological implications? In the field of physics of computation, it has been argued that all computations can be done without spending energy, by way of *reversible computing* [84]. A theoretical example of such a reversible computer is the “billiard ball computer”, in which frictionless motion of colliding classical balls accomplishes any computation without spending energy. Of course there is a “catch”: The billiard ball computer is extremely sensitive to an external force, internal friction and so on; and its dynamics is essentially chaotic. To make it work, one has to set up feedback systems to *measure* the positions of the balls, and if a ball goes away from the supposed trajectory, the feedback system should gently push the ball back on the track. However, measurement entails measured data stored in a memory, which eventually need to be discarded. Then, the Landauer-Sagawa-Ueda theorem [85, 86] states that heat must be generated in this whole process of measurement and memory erasure, or in other words entropy must be thrown away. One question associated with this is whether or not the chaotic motion of a reversible computer can be suppressed quantum mechanically at least partially, thus reducing the reliance on feedback systems. *If* that is possible, a fascinating question then is whether or not such a mechanism is at work in biological systems to maintain their “orderly dynamics” without generating excessive heat.

Apart from these speculations, even if the hypothesis studied in this work — the classically chaotic dynamics of molecules in the cell is suppressed quantum mechanically — turns out to be plain wrong (and there is a good chance to be so), the following idea should be independent from that: There can be a classically chaotic system, which is microscopic in the sense we discussed, whose internal dynamics is highly unobservable from the outside, whose chaotic motion is quantum mechanically suppressed before decoherence sets in, and which operates quantum mechanically outside the traditional domain of quantum systems. Such an engineered system, if built, could find useful applications that might include ultralow-power computing.

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²¹Strictly speaking, showing the impossibility to efficiently simulate a quantum chaotic system with a classical computer amounts to proving $BPP \neq BQP$, which is regarded difficult.

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